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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.							
10/620,052	07/14/2003	Yasumichi Hitoshi	021044-004010US	7655							
20350	7590 08/04/2006		EXAMINER								
	ID AND TOWNSEND ARCADERO CENTER	HALVORSON, MARK									
EIGHTH FL		ART UNIT PAPER NUM									
SAN FRANC	CISCO, CA 94111-383	1642									

DATE MAILED: 08/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

•		Applica	ition No.	Applicant(s)	Applicant(s)								
		10/620		HITOSHI ET AL.									
	Office Action Summary	Examin	ier	Art Unit									
		Mark Ha	alvorson	1642									
Period fo	The MAILING DATE of this communication	tion appears on t	the cover sheet	with the correspondence ac	dress								
A SH WHIC - Exter after - If NO - Failu Any I	ORTENED STATUTORY PERIOD FOR CHEVER IS LONGER, FROM THE MAIL asions of time may be available under the provisions of 3' SIX (6) MONTHS from the mailing date of this communic period for reply is specified above, the maximum statuto re to reply within the set or extended period for reply will, reply received by the Office later than three months after the patient term adjustment. See 37 CFR 1.704(b).	ING DATE OF 7 CFR 1.136(a). In no ation. ry period will apply and by statute, cause the a	THIS COMMUN event, however, may d will expire SIX (6) Mapplication to become	NICATION. a reply be timely filed ONTHS from the mailing date of this c ABANDONED (35 U.S.C. § 133).									
Status													
1\⊠	Responsive to communication(s) filed of	n 12 lune 2006	1	•									
2a)□	Responsive to communication(s) filed on <u>12 June 2006</u> . This action is FINAL . 2b) This action is non-final.												
, —	Since this application is in condition for allowance except for formal matters, prosecution as to the merits is												
٠,١	closed in accordance with the practice under <i>Ex parte Quayle</i> , 1935 C.D. 11, 453 O.G. 213.												
Dispositi	on of Claims	•	•	, , , , , , , , , , , , , , , , , , ,									
•	Claim(s) <u>1-44</u> is/are pending in the appli	lication											
•	4a) Of the above claim(s) <u>3-6,10,13,14</u> ;		4-44 is/are with	drawn from consideration									
	Claim(s) is/are allowed.	.,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	<u> </u>										
•	Claim(s) <u>1, 2, 7-9, 11, 12, 15, 16, 18 an</u>	d 23 is/are reie	cted										
· ·	Claim(s) is/are objected to.	<u>u 20</u> 10/4/0 10/0											
•	Claim(s) are subject to restriction	n and/or election	requirement.										
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• •	on Papers												
•	The specification is objected to by the E												
10)	The drawing(s) filed on is/are: a)												
	Applicant may not request that any objection												
	Replacement drawing sheet(s) including the												
11)	The oath or declaration is objected to by	the Examiner.	Note the attach	ed Office Action or form P	10-152.								
Priority ι	ınder 35 U.S.C. § 119												
a)	Acknowledgment is made of a claim for All b) Some * c) None of: 1. Certified copies of the priority doc 2. Certified copies of the priority doc 3. Copies of the certified copies of the application from the International See the attached detailed Office action for	cuments have be cuments have be he priority docu Bureau (PCT R	een received. een received in ments have bee Rule 17.2(a)).	Application No en received in this National	l Stage								
2) 🔲 Notic 3) 🔯 Infori	t(s) e of References Cited (PTO-892) e of Draftsperson's Patent Drawing Review (PTO- mation Disclosure Statement(s) (PTO-1449 or PTO- r No(s)/Mail Date 1/29/2004; 11/18/2		Paper N 5) Notice of	w Summary (PTO-413) lo(s)/Mail Date of Informal Patent Application (PT requence search.	O-152)								

DETAILED ACTION

Election/Restrictions

1. Applicants election with traverse of Group 1 is acknowledged. Applicant's selection of polypeptides related to SEQ ID N0:l4 is acknowledged. Applicants selection of the following species is acknowledged: (ii)(a) nuclease activity; (ii)(b) fluorescent marker level; (ii)(b)(II) cell tracker dye; (iii) transformed cell line; (iiie) A549; and (iv) a small organic molecule.

Beth Kelly of Townsend, Townsend and Crew was called on July 19, 2006 to further select one of two species, (ii)(a) nuclease activity or (ii)(b) fluorescent marker level. Beth Kelly selected (ii)(a) nuclease activity.

The traversal is on the ground(s) that the inventions have not been shown to be unrelated and the examination of all groups would not impose a serious burden on the examiner. Applicant's assert that Group 2 and 3, directed to a method of modulating cell cycle arrest using a compound that modulates the cell cycle or a target protein for modulation of the cell cycle; and Group 1 directed to a method of identifying a compound that modulates cell cycle arrest by contacting a cell that comprises a target polypeptide with the compound, as the required compositions of Group 1 are also found in Groups 2 and 3. This response is not found persuasive. MPEP 802.01 provides that restriction is proper between inventions which are independent or distinct. Here, the

inventions of the various groups have been shown to be distinct as set forth in the restriction of June 12, 2006. Claim 24 of Group 2 and Claim 34 of Group 3 do depend on claim 1 but only to the extent that it uses the compound identified by claim 1 and furthermore, claim 24 and claim 34 are directed to in vivo use. Also, as previously mentioned in the Office Action of May 8, 2006 the materially distinct inventions of Group 1-3 differ in objectives, method steps and reagents.

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As to the question of burden of search, the inventions are classified differently, necessitating different searches in different class/subclasses. Further, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not coextensive and is much more important in evaluating the burden of search (art here is cancer therapy). Different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper.

Claims 1-44 are pending in the application and Claims 3-6, 10, 13, 14, 17, 19-22 and 24-44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on June 12, 2006. Claims 1, 2, 7-9, 11, 12, 15, 16, 18 and 23 are currently under prosecution.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

- 2. Claims 1, 2, 7-9, 11, 12, 15, 16, 18 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "hybridizes under stringent conditions" are indefinite because it is not clear what is meant by these terms. To overcome this rejection the conditions for the hybridization, including the wash step, must be incorporated into claims 1 and 23, provided written support for such an amendment exists.
- 3. Claims 1, 2, 7-9, 11, 12, 15, 16, 18 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps is describing how the identification of a compound that modulates cell cycle arrest can be obtained based on the determination of a chemical or phenotypic effect of that compound upon the cell.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 2, 7-9, 11, 12, 15, 16, 18 and 23 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

The claims are drawn to a method for identifying a compound that modulates cell cycle arrest, the method comprising the steps of: (i) contacting a cell comprising a target compound consisting of a flap structure specific endonuclease 1 (FEN1) or <u>fragment</u> thereof or inactive variant thereof, the target polypeptide encoded by the complement of a <u>nucleic acid that hybridizes under stringent conditions</u> to a nucleic acid encoding <u>a</u> polypeptide having an amino acid sequence of SEQ ID NO:14; and (ii) determining the chemical or phenotypic effect of the compound upon the cell comprising the target polypeptide or fragment thereof or inactive variant thereof, thereby identifying a compound that modulates cell cycle arrest.

The specification describes two dominant negative mutants of FEN1 and demonstrates that the expression of two FEN1 dominant negative mutants are antiproliferative in A549 and H1299 cells (see Figures 66-68).

The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in <u>University of California v. Eli Lilly and Co.</u>, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials." Id. The court in <u>Enzo</u> adopted the standard that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant

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identifying characteristicsi.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. (Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 1324; 63 USPQ2d 1609, 1613 (Fed. Cir. 2002)). (emphasis omitted, bracketed material in original).

Thus, the instant specification may provide an adequate written description of flap structure specific endonuclease 1 (FEN1) or fragment thereof or inactive variant, per Lilly by structurally describing a representative number of peptides that function as claimed or by describing structural features common to the members of the genus, which features constitute a substantial portion of the genus. Alternatively, per Enzo, the specification can show that the claimed invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

In this case, the specification does not describe the genus of peptides of flap structure specific endonuclease 1 (FEN1) or <u>fragment thereof or inactive variants</u>

thereof in a manner that satisfies either the <u>Lilly</u> or <u>Enzo</u> standards. There are insufficient structural features common to all members of the genus of peptides of flap structure specific endonuclease 1 (FEN1) or <u>fragment thereof or inactive variants</u> thereof.

Variants include conservatively modified variants which are defined in the specification as substitutions, deletions or additions to a protein sequence which alters,

adds or deletes a single amino acid or a small percentage of amino acids in the encoded sequence is a "conservatively modified variant" where the alteration results in the substitution of an amino acid with a chemically similar amino acid (paragraph 133). Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles of the invention.

Fragments of polypeptides are not specifically defined in the specification but theoretically could be a multitude of different peptides. "Fragment" reads on a peptide as small as 2 amino acids to as long as 380 amino acids. Applicant has not identified which domain(s) in the protein is/are needed for interaction between the polypeptide and small molecule. Even if such domains are identified for one type of modulator there is no objective evidence to show that this is the domain for interaction for all the different types of small molecules.

Furthermore, there are an unknown number of polypeptides encoded by the complement nucleic acid strand of a nucleic acid that hybridizes under stringent conditions to a nucleic acid encoding a polypeptide having an amino acid sequence of SEQ ID NO:14. This encompasses a complement nucleic acid strand of a nucleic acid that hybridizes to a nucleic acid encoding a polypeptide. A nucleic acid encoding a polypeptide having an amino acid sequence of SEQ ID NO:14 reads on a dipeptide consisting of two contiguous amino acids of SEQ ID NO:14.

In addition, a polypeptide encoded by a nucleic acid comprising a sequence of SEQ ID NO:13 reads on a dipeptide consisting of two amino acids encoded by contiguous nucleotides of SEQ ID NO:13.

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The genus of target polypeptides encompassed by claims 1,2 7-9, 11, 12, 15, 16, 18 and 23 consists of a multitude of peptides. The only common structural feature of all the species of that contain at least two contiguous amino acids in common with SEQ ID NO:14. Three species, the peptide of SEQ ID NO:14 and two dominant negative mutants does not adequately define the genus of peptides encompassed by claims 1, 2, 7-9, 11, 12, 15, 16, 18 and 23. Thus the claimed peptides do not meet the standard set forth in Lilly.

The instant specification may also provide an adequate written description of the target polypeptide if the specification can show that the claimed invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. The specification discloses three species, the peptide of SEQ ID NO:14 and two dominant negative mutants. The genus of peptides encompassed by claims 1, 2, 7-9, 11, 12, 15, 16, 18 and 23 are FIN1, fragments of FIN1, inactive variants of FIN1 and polypeptides encoded by the complement nucleic acid of a nucleic acid that hybridizes under stringent conditions to a nucleic acid encoding a polypeptide having an amino acid sequence of SEQ ID NO:14. There is insufficient information as to which amino acids can function as contemplated in the specification or even what positions are critical for these functions. Its not clear if amino acids can be randomly inserted into any amino acid position of FIN1 or if there is directed insertions of amino acids at these positions. Thus, the specification does not sufficient structural characteristics that correlate with the ability of the peptide to function

as contemplated by the specification and for the reasons set forth above do not meet the standards set forth by Enzo.

Thus, the specification does not provide an adequate written description of the genus of peptides of claims 1, 2, 7-9, 11, 12, 15, 16, 18 and 23 that is required to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
- 5. Claims, 1, 2, 7, 8, 15, 16, 18 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Harrington et al (US Patent No: 5, 874, 283, issued February 23, 1999).

The claims are drawn to a method for identifying a compound that modulates cell cycle arrest, the method comprising contacting a cell comprising a target compound consisting of a flap structure specific endonuclease 1 (FEN1) and determining the chemical or phenotypic effect of the compound upon the cell, thereby identifying a compound that modulates cell cycle arrest wherein modulation is activation of cancer cell cycle arrest, wherein the polypeptide is recombinant, wherein the polypeptide is encoded by a nucleic acid comprising SEQ ID NO:13, wherein the compound is a small organic molecule.

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Harrington et al disclose a method for identifying modulating agents of the FEN-1 peptide of SEQ ID NO:14 (see Sequence Search) which reduce the cell's capacity to repair DNA damage or inhibit endogenously naturally-occurring FEN1 (column 39 lines 25-28). These modulating agent are candidate neoplastic agents which can be tested further for antineoplastic activity. Harrington et al further disclose that the present invention may be used to design drugs that inhibit the binding of FEN1 to DNA flaps or nicks and to catalyze nuclease activity on the flap strand (column 42 lines 58-61). The nucleic acid of SEQ ID NO:13 encodes the peptide of SEQ ID NO:14.

In addition Harrington et al teach a recombinant FIN1 polypeptide used in a yeast two hybrid system to detect compounds that bind to FIN1 to identify candidate FEN-1 modulatory agents. (column 36 line 62 to column 39 line 24). Enzymatic activity is used to detect binding of a compound to FIN1 (Id).

6. Claims 1, 9, 11, 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Bai et al (FEBS letters 437:61-64,1998).

The claims are drawn to a method for identifying a compound that modulates cell cycle arrest, the method comprising contacting a cell comprising a target compound consisting of a flap structure specific endonuclease 1 (FEN1) and determining the chemical or phenotypic effect of the compound upon the cell, thereby identifying a compound that modulates cell cycle arrest, wherein he cell is the transformed cancer cell line A549.

<u>Bai et al</u> disclose that the treatment of the adenoma cancer cell line A549 with the small molecule flavone results in the inhibition of proliferation and cell cycle arrest of the A549 cell line. The A549 cell line inherently expresses FIN1.

Summary

- 7. No claims allowed.
- 8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Halvorson, PhD whose telephone number is (571) 272-6539. The examiner can normally be reached on Monday through Friday from 8:30am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mark Halvorson, PhD Patent Examiner 571-272-6539

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1	emience 150	quence 15	equence 388,	equence 286,	equence 155,	equence 155,	equence 272,	equence 141,	equence 14	equence 397,	equence 5910,	Sequence 340, App	equence 336,	equence 401, Ap	equence 78	equence 78	equence 78	equence 11	equence 11	equence 11	1	78	17	ພູ	w w	_	<u>.</u>	ω. Έ.	7	e .	equence 1.	equence 1.	equence 5,	equence 5,	equence 3,	quence 3,	equence 6,	

ALIGNMENTS

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US-08-455-968B-2
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APPLICANT: Harring
                                                                                                                                                                                                                                                              ZIP: 94111-3834
COMPUTER READABLE FORM:
MEDIUM TYPE: Floppy disk
ATTORNEY/AGENT INFORMATION:
NAME: Apple, Randolph T.
REGISTRATION NUMBER: 36,429
REFERENCE/DOCKET NUMBER: 19985-000100
TELECOMMUNICATION INFORMATION:
                                                                                                                                 CURRENT APPLICATION DATA:
APPLICATION NUMBER: US
FILING DATE: 30-MAY-19
                                                                                                                                                                                                                                                                                                                                                                                     CORRESPONDENCE ADDRESS:
ADDRESSEE: Townsend and Townsend and Crew LLP STREET: Two Embarcadero Center, 8th Floor
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  APPLICANT: Hsieh, Chin-Lin
APPLICANT: Lieber, Michael
TITLE OF INVENTION: Mammal
                                                                                                                                                                                                                                                                                                                                                                                                                                                                  NUMBER OF SEQUENCES:
                                                                                                                                                                                   COMPUTER: IBM PC compatible
OPERATING SYSTEM: PC-DOS/MS-DOS
SOPTWARE: Patentin Release #1.0, Version #1.25
                                                                                                                                                                                                                                                                                                                                                                         CITY: San Francisco
                                                                                                      FILING DATE: 30-MAY-1995
CLASSIFICATION: 435
                                                                                                                                                                                                                                                                                                                                COUNTRY:
                                                                                                                                                                                                                                                                                                                                                       California
                                                                                                                                                                                                                                                                                                                                     USA
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Heieh, Chih-Lin
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TELEFAX: 415-576-0300
INFORMATION FOR SEQ ID NO:
SEQUENCE CHARACTERISTICS:

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Percent Similarity:
Best Local Similarity:
Query Match:
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STRANDEDNESS: single
TOPOLOGY: linear
MOLECULE TYPE: CDNA
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ArgArgLeuAspProAsnLysTyrProValProGluAsnTrpLeuHisLysGluAlaHis
                                                                                                 GluGlnPheValAspLeuCysIleLeuLeuGlySerAspTyrCysGluSerIleArgGly
                                                                                                                                                    LysLeuProIleGlnGluPheHisLeuSerArgIleLeuGlnGluLeuGlyLeuAsnGln
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                                          | IleGlyProLysArgAlaValAspLeuIleGlnLysHisLysSerIleGluGluIleVal
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                             ATTGGGCCCAAGCGGGCTGTGGACCTCATCCAGAAGCACAAGAGCATCGAGGAGATCGTG
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                          Best Local Similarity:
                                                  Score:
        Query Match:
                                     Percent Similarity:
                                                                                                           US-08-455
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           Sequence 2
Patent No.
                                                                                                                                                                                                                                                                        COUNTRY: USA
ZIP: 94111-3834
COMPUTER READABLE FORM:
MEDIUM TYPE: Ploppy disk
COMPUTER: IBM PC compatible
COMPUTER: IBM PC compatible
OPERATING SYSTEM: PC-DOS/MS-DO
SOFTWARE: PatentIn Release #2 //
CURRENT APPLICATION DATA:
APPLICATION NUMBER: US/08 55,96
FILING DATE: 30-MAY-1995
FILING DATE: 30-MAY-1995
CLASSIFICATION: 435
ATTORNEY/AGENT INFORMATY A:
NAME: Apple, Randoly T.
REGISTRATION NUMBER: 36,429
REGISTRATION NUMBER: 36,429
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INFORMATION FOR
SEQUENCE CHAR
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TITLE OF INVENTION: Mammalian Flap-Specific
NUMBER OF SEQUENCES: 63
CORRESPONDENCE ADDRESS:
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     APPLICANT: Harrington, John APPLICANT: Hsieh, Chih-Lin APPLICANT: Lieber, Michael
                                                                                                                                                                                                                                              TELECOMMUNICATION
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   ADDRESSEE: Townsend and Townsend STREET: Two Embarcadero Center, 8 CITY: San Francisco
                                                                                                                                                                                                                                                              REFERENCE/DOCKET
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                                                                                                                                                                             LENGTH:
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           Length:
Matches:
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